Response, Applicants have amended Claim 1 and cancelled Claims 9, 10, 29, and 30, without prejudice. Applicants reserve the right to pursue the originally filed, similar and/or broader claims in one more subsequently filed applications.

The Examiner has objected to the Specification for failing to recite the related applications for which the present application claims benefit. Also, the Examiner has objected to the disclosure of page 15, line 19, for lacking the formulation for an "R factor," as provided in the earliest application serial number 09/060,872. Applicants have amended the Specification to indicate the priority claims and have amended page 15, to provide the formula for the "R factor." As these amendments find support in Specification, accompanying filing documents, and priority applications, Applicants respectfully submit that no new matter is added in these amendments. The Examiner has further indicated that should Claim 7 be found allowable, that Claim 30 would be objected to under 37 CFR §1.75 as being a substantial duplicate thereof. In order to further their business interests and the prosecution of the present application, Applicants have cancelled Claim 30 without prejudice. Applicants have also added new Claim 31, which recites at least one T-cell epitope and the alteration of at least one T-cell epitope to provide a variant. Support for this new Claim is found throughout the Specification as filed. No new matter is added in this new Claim. The Examiner's rejections are addressed in the following order:

1) Claims 9-10 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite;

2) Claims 9-10 and 29 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly not meeting the written description requirement;

3) Claims 9-10 and 29 stand rejected under 35 U.S.C. §101;

4) Claims 1, 4-5, 7, and 29 stand rejected under 35 U.S.C. §102(a), as allegedly being anticipated by Landry (WO 99/06061); and

5) Claims 1, 4, 7, and 30 stand rejected under 35 U.S.C. §102(a), as allegedly being anticipated by Mouritsen *et al.* (WO 95/05898).

1) The Claims are Definite

The Examiner has rejected Claims 9-10 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. In particular, the Examiner indicates that the recitation "said polypeptide of interest and said homologue combined" is unclear, because there is nothing recited as being "combined" in base Claim 8. Applicants have cancelled Claims 9 and 10

without prejudice. Applicants reserve the right to pursue the originally filed, similar and/or broader Claims in one or more additional applications. As these Claims have been cancelled, Applicants respectfully submit that this rejection is moot and should be withdrawn.

2) The Written Description Requirement is Met

The Examiner has rejected Claims 9-10 under 35 U.S.C. §112, first paragraph, as allegedly not meeting the written description requirement. The Examiner argues that "Applicant did not have possession of any proteins which have been altered by the elimination of one or more T-cell epitopes, as required by claims 9-10, and which also have a greater immunogenicity than the unaltered protein, as required by base claim 1." (Office Action, page 4). Applicants must respectfully disagree with the Examiner's statement. Nonetheless, as indicated above, Applicants have cancelled Claims 9 and 10 without prejudice. Applicants reserve the right to pursue the originally filed, similar and/or broader Claims in one or more additional applications. As these Claims have been cancelled, Applicants respectfully submit that this rejection is moot and should be withdrawn.

3) The Claims Meet the Requirements for Patentable Material

The Examiner has rejected Claims 9-10 and 29 under 35 U.S.C. §101. The Examiner indicates that these Claims are rejected "because base claim 1 requires that the polypeptide have its T-cell epitope(s) be altered such that a greater immunogenic response is obtained than would be obtained with a polypeptide having an unaltered T-cell epitope." (Office Action, page 3). As indicated above, Applicants have cancelled Claims 9 and 10 without prejudice; Applicants have also cancelled Claim 29 without prejudice. Applicants reserve the right to pursue the originally filed, similar and/or broader Claims in one or more additional applications. As these Claims have been cancelled, Applicants respectfully submit that this rejection is moot and should be withdrawn.

4) The Claims Are Novel Over Landry

The Examiner has rejected Claims 1, 4-5, 7, and 29 under 35 U.S.C. §102(a), as allegedly being anticipated by Landry (WO 99/06061). The Examiner argues that "Landry shows altered proteins, which are modified at a T-cell epitope by virtue of insertion (usually N-terminally adjacent thereto, or partially overlapping the N-terminal) of an unstable (i.e. flexible) peptide segment." (Office Action, page 5). The Examiner indicates that Claim 4 has been rejected because Landry teaches vaccines; Claim 5 has been rejected because gp120 is a

protein from an infectious virus which is "exogenous" to an infected individual; and Claim 7 is included since insertions taught by Landry encompass substitution (Office Action, page 5).

Applicants must respectfully disagree with the Examiner's arguments. Nonetheless, Applicants respectfully submit that Landry is NOT prior art. The present application claims priority to co-pending U.S. Patent Application Serial Number 09/500,135, which was filed on February 8, 2000. This "parent" application provides disclosure of altered proteins which are modified at a T-cell epitope and that exhibit a greater immune response that the original protein (*See e.g.*, page 5, lines 9-10; page 6, lines 8-10; and page 14, lines 13-14). In addition, this parent application provides support for the use of modified epitopes for production of vaccines (*See e.g.*, page 5, lines 14-25; page 6, lines 11-13; and page 15, lines 5-9, and 13-15). Thus, the presently claimed subject matter of Claims 1, 4-5, 7 and 29, is entitled to the priority date of parent application serial number 09/500,135. Because the parent application was filed less than one year after the publication of the Landry reference, the Landry reference is not a statutory bar under 35 U.S.C. §102(b). As indicated in the accompanying Declaration of Fiona Harding, filed herewith, the claimed subject matter was invented prior to the publication date of the Landry reference (February 11, 1999). Thus, the Landry reference is not prior art and is not a proper reference under 35 U.S.C. §102(a). Thus, Applicants respectfully request that this rejection be withdrawn.

5) The Claims Are Novel Over Mouritsen *et al.*

The Examiner has rejected Claims 1, 4, 7, and 30 under 35 U.S.C. §102(a), as allegedly being anticipated by Mouritsen *et al.* (WO 95/05898). In particular, the Examiner argues that "Mouritsen et al. disclose immunogenic forms of self-proteins (e.g., cytokines listed in the Para. Spanning pages 7-8), in which residues within the self-protein have been substituted with residues from a foreign (i.e., heterologous) T-cell epitope. These modified proteins are more immunogenic than the unmodified self-protein." (Office Action, page 6). Applicants must respectfully disagree with the Examiner's characterization of the pending Claims. Independent Claims 1 and 30 clearly recite that the variant protein has an altered T-cell epitope (*i.e.*, an endogenous T-cell epitope). This is in contrast to the *insertion* of *foreign* T-cell epitopes in a recombinant protein. Mouritsen *et al.* teach the insertion of one or more foreign T-cell epitopes in recombinant proteins such that a profound autoantibody response is produced against the proteins (*See e.g.*, page 6, lines 29-33). While Applicants believe that the originally claimed invention is patentably distinct over Mouritsen *et al.*, in order to further their business interests

and the prosecution of the present application, yet without acquiescing to the Examiner's arguments, Applicants have amended the Claims to recite that the T-cell epitope is modified. Applicants reserve the right to pursue the originally filed and/or broader Claims in one or more additional applications. As Mouritsen *et al.* do not teach modification of T-cell epitopes as presently claimed, Applicants respectfully submit that the Claims are novel over Mouritsen *et al.*, and request that this rejection be withdrawn.

CONCLUSION

In light of the above remarks, the Applicants believe the pending claims are in condition for allowance and issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 846-5838.

Respectfully submitted,

Date: 12 June 2003

Kamrin T. MacKnight
Registration No. 38,230

Genencor International, Inc.
925 Page Mill Road
Palo Alto, CA 94304
Tel: 650-846-5838
Fax: 650-845-6504

APPENDIX I
MARKED-UP VERSION OF SPECIFICATION'S REPLACEMENT PARAGRAPHS AND REWRITTEN, ADDED, AND/OR CANCELLED CLAIMS

The following is a marked-up version of the specification's replacement paragraphs pursuant to 37 C.F.R. §1.121(b), as well as a marked-up version of the claims pursuant to 37 C.F.R. §1.121 (c)(1)(ii) with instructions and markings showing changes made herein to the previous version of record of the specification and claims. Underlining denotes added text while bracketing denotes deleted text.

IN THE SPECIFICATION:

On page 1, under "CROSS-REFERENCE TO RELATED APPLICATIONS" please replace the current paragraph with the following paragraph:

[This application is a continuation-in-part of USSN 09/500,135, filed April 2, 2000, which is a continuation-in-part of USSN 09/060,872, filed April 15, 1998, both of which are incorporated by reference in their entireity.]

The present application is a Continuation-in-Part of U.S. Patent Application Serial Number 09/500,135, filed February 8, 2000, which is a Continuation-in-Part of U.S. Patent Application Serial Number 09/060,872, filed April 15, 1998. The present application is also related to U.S. Patent Application Serial Numbers 09/255,502, 09/255,505, and 09/255,501, all of which were filed February 23, 1999, and are Divisionals of U.S. Patent Application Serial Number 09/060,872, filed April 15, 1998.

On page 15, following line 19 and before line 20, please insert the following formula:

$$-- R\,factor = \frac{\Sigma_h |Fo(h)| - |Fc(h)|}{\Sigma_h |Fo(h)|} --$$

IN THE CLAIMS:

Please cancel Claims 9, 10, 29, and 30.

Please amend Claim 1 as follows and add new Claim 31.

1. (Twice Amended) A variant of a polypeptide of interest comprising a T-cell epitope, wherein said variant differs from said polypeptide of interest by having an altered T-cell epitope such that said variant produces an immunogenic response in an individual which is

greater than the immunogenic response produced by said polypeptide of interest, wherein said T-cell epitope of said polypeptide of interest is altered to produce said variant.

31. (New) A variant of a polypeptide of interest comprising at least one T-cell epitope, wherein said variant differs from said polypeptide of interest by having at least one altered T-cell epitope, such that said variant produces an immunogenic response in an individual which is greater than the immunogenic response produced by said polypeptide of interest, wherein said at least one T-cell epitope of said polypeptide of interest is altered to produce said variant.

APPENDIX II

CLEAN VERSION OF THE ENTIRE SET OF PENDING CLAIMS AS AMENDED IN THIS COMMUNICATION

The following is a list of the Claims as they would appear following entry of this amendment.

1. (Twice Amended) A variant of a polypeptide of interest comprising a T-cell epitope, wherein said variant differs from said polypeptide of interest by having an altered T-cell epitope such that said variant produces an immunogenic response in an individual which is greater than the immunogenic response produced by said polypeptide of interest, wherein said T-cell epitope of said polypeptide of interest is altered to produce said variant.

4. The variant of claim 1 wherein said polypeptide of interest is selected from the group consisting of enzymes, hormones, factors, vaccines and cytokines.

5. The variant of claim 1 wherein said polypeptide of interest is not recognized by said individual as endogenous to said individual.

6. The variant of claim 1 wherein said polypeptide of interest is an enzyme selected from the group consisting of lipase, cellulase, endo-glucosidase H, protease, carbohydrases, reductase, oxidase, isomerase, transferase, kinase and phosphatase.

7. The variant of claim 1 wherein said T-cell epitope is altered with amino acid substitutions.

8. (Once Amended) The variant of claim 1 wherein said T-cell epitope is altered by having a terminal portion of said polypeptide of interest comprising said T-cell epitope replaced with a corresponding terminal portion of a homolog of said polypeptide of interest wherein said homolog does not comprise a T-cell epitope identical to said replaced T-cell epitope.

31. (New) A variant of a polypeptide of interest comprising at least one T-cell epitope, wherein said variant differs from said polypeptide of interest by having at least one altered T-cell epitope, such that said variant produces an immunogenic response in an individual which is greater than the immunogenic response produced by said polypeptide of

interest, wherein said at least one T-cell epitope of said polypeptide of interest is altered to produce said variant.